## REMARKS

Claims 1-18 and 20-34 are pending in the present application.

### Claim Objections

The numbering of claims was not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. Applicants appreciate that misnumbered claims 19-33 have been renumbered as claims 20-34, respectively, because claim 19 was cancelled in the amendment filed January 30, 2001 (Paper No. 5). Applicants provide herewith a clean copy of all pending claims as the Examiner requested.

### Rejection under 35 U.S.C. § 112

The Examiner rejects claims 1-18 and 20-33 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not properly described in the specification. Independent claims 1 and 18 were amended to add the limitation "the pharmaceutical agent being solubilized in the composition but insoluble in both water and the occlusive agent" and claim 20 was amended to add the limitation "the pharmaceutical agent being solubilized in the composition but insoluble in both water and petrolatum."

The Examiner admits that the specification, at page 2, lines 9-18, provides antecedent basis for the active ingredient being insoluble in both water and the occlusive agent. However, the Examiner maintains that the specification does not appear to provide antecedent basis for the active ingredient being solubilized in the composition but not soluble in both water and the occlusive agent. According to the Examiner, one skilled in the art would not expect an active ingredient that is insoluble in both hydrophobic and hydrophilic environments to be solubilized in the composition, particularly without a surfactant or emulsifier.

Applicants respectfully traverse. The specification clearly infers such a feature. The present specification teaches formulations having " an organic cosolvent" as is recited in independent claims 1, 18, and 20. An organic cosolvent would not be required if the

pharmaceutically active ingredient was suspended in a composition instead of being dissolved. Thus the stipulation that an effective amount of "an organic cosolvent" is essential for the invention indicates that the active ingredient is dissolved in the composition. If an active agent is soluble in water or a petrolatum/mineral oil, then a cosolvent would not be required and would not be included in the composition. Stated differently, the very presence of an organic cosolvent is evidence for the "pharmaceutical agent being solubilized in the composition but insoluble in both water and the occlusive agent."

The Examiner will readily appreciate that the exemplified active ingredient in the present specification, namely clobetasol is soluble in cloroform. (See, Sigma specification, submitted herewith as Exhibit C). This suggests it is ***not*** soluble in water.

**Claim Rejections - 35 U.S.C. § 103**

***Rejection under 35 U.S.C. §103(a) over Davis in view of Woodford, et al.***

Claims 1-10, 12-14, 16-18, 20-26, 28-30, and 32-33 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Davis (US 5,143,717) and further in view of Woodford, *et al.*, "Bioavailability and Activity of Topical Corticosteroids from a Novel Drug Delivery System, the Aerosol Quick-Break Foam," *J. Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

*Davis*

Applicants reiterate that Davis discloses an antibiotic formulation useful in the treatment of burns and abrasions and adapted for topical application as a foam. Specifically, the Davis formulation is "an antibiotic [silver sulfadiazine] ***suspended*** in an oil-in-water emulsion that includes specific quantities of white petrolatum, a fatty alcohol, an emollient, an emulsifying agent, a humectant, a preservative and water." (Column 1, lines 63-68; *See also e.g.*, column 2, lines 18-27.) Thus, ***the active ingredient in Davis***, specifically silver sulfadiazine, ***is suspended***

in the formulation. (*See*, e.g. Harding Declaration, paragraph 4) This is further evidenced by the extensive discussion in Davis regarding the micelle-like bubble architecture of the Davis foam. (*See* column 2, line 62 *et seq.*) Further information distinguishing micelle suspensions from solutions is provided in the Harding Declaration at paragraph 9, submitted herewith. Another important feature of the Davis foam is that it remains stable over long periods of time, i.e., "at least 24 hours after being applied." (column 4, lines 18-24.)

In order to provide supplemental evidence of this fact, Applicants have reviewed the publicly available file history of the prosecution of the Davis patent ('717 patent). First, Applicants respectfully direct the Examiner's attention to the Declaration of Richard C. Davis under Rule 132 received in the USPTO on August 15, 1991, submitted herewith as Exhibit A. Particularly, Applicants direct the Examiner's attention to the following statements of the inventor and now patentee, under oath:

> It was told to me over the phone.....that silver sulfadiazine, as a molecular entity, is biphasic having a hydrophilic end and a hydrophobic end. Because of this, I was told, it was impossible to get the chemical to dissolve in either a lipid solution solvent or in water. Sometime after that, I conceived the idea of trying to place the antibiotic (silver sulfadiazine) in a foam having a micellar-like bubble structure." (Page 2, lines 8-15)
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> **********
>
> Using the microscope, I observed a high degree of material in peripheral aspects of the bubbles of the foam and that none of the material had invaded the interior surface of the bubble. This indicated to me that I had in fact achieved a stable micellar structure with the silver sulfadiazine molecules, used as a "lock and key mechanism", being oriented perpendicularly (radially) throughout the very small bubble membranes with the water soluble ends thereof directed outwardly. (Page 3, lines 16-24)
>
> **********
>
> By utilizing the "lock and key mechanism" of the silver sulfadiazine molecule, a linear, relatively straight, chain entity with a water soluble end and a lipid soluble end to provide a coupling at the gas/oil/water suspension interface "the wall of the bubble" and to reduce the mobility of those substances at that point, the stability of the foam has been experimentally observed to increase tremendously. This "locking" by the silver sulfadiazine molecule reduces the mobility of other substances at that point and therefore maintains the integrity of the surface of the bubbles, i.e. the formation of stable bubbles. (Page 4, line 18- Page 5, line 2)

Second, Applicants respectfully direct the Examiner's attention to the First Rule 131 Declaration of the inventor and now patentee, Richard C. Davis, signed on July 10, 1991, submitted herewith as Exhibit B. In the subject Declaration, the inventor, now patentee, refers to a document entitled "Draft Patent Background for Silvafoam", prepared prior to September 23, 1987, a copy of which is submitted together with the Rule 131 Declaration by the the Declarant. Applicants respectfully direct the Examiner's attention to page 3 of that document where "Micelles" are discussed in depth. Particularly, the following comments indicate that a micelle cannot be the same as a solute suspended in solution.

> A micelle is the fundamental structure of all living things. Basically a micelle is a hollow chamber surrounded by a surface.....to create stable architecture, facilitate transport of substances across the membrane, and many other complex functions.
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> **********
>
> Micelles on the other hand, have a membrane which has little pores all over it designed for controlled leakage, into and out of the cell.
>
> **********
>
> The micelle membrane then acts like a barrier separating water-loving and water-hating environments and the complex chemical reactions that take place in both.

Third, Applicants respectfully direct the Examiner's attention to the Declaration of Ronald Harding, submitted herewith. Mr. Harding clarifies that a suspension of micelles is not a solution as follows:

> Micelles are organised aggregates of surfactant molecules (as explained in Appendix 6, submitted herewith) and can form many shapes, for example spheres, tubes, layers as aggregates, vesicles and lamella. Typically in less concentrated solutions micelles form spherical aggregates or vesicles, which will be in the form of a dispersed phase within the continuous phase. (Harding Declaration, paragraph 9)

*Davis in view of Woodford et al.*

Applicants note that the recited combination, i.e., the foam of Davis modified by adding the corticosteroid of Woodford, *et al.*, does not yield the claimed formulations. As noted above,

Davis teaches a ***suspended*** active ingredient, not a ***solubilized*** active ingredient, as is claimed. Davis does not teach that it would be desirable, or even possible, to solubilize the particular active ingredient. Further, the addition of the corticosteroid of Woodford *et al.* would not change the essence of the Davis foam, i.e., an emulsion of a suspended active.

One skilled in the art would readily appreciate that formulations of solublized active ingredients have a variety of potential advantages over suspended actives, including increased stability, faster penetration, better distribution of active ingredient throughout the formulation, better compatibility with solvent systems and surfactants, and better cosmetic feel. (*See*, Harding Declaration, paragraph 8) Suspended active ingredients suffer from comparative disadvantages, including likelihood of a potential to aggregate or "settle out" of the formulation, slower penetration, a need to add suspending agents, incompatibility with certain solvent systems and surfactants, and a potential gritty sensation when applied. Hence, a formulation having a solubilized active ingredient cannot be the same as a formulation having a suspended active ingredient.

*The Examiner's Position*

The Examiner maintains that Woodford *et al.* teach solubilizing the corticosteroid in alcohol, thus meeting the limitation of "the pharmaceutically active ingredient being solubilized in the composition." (citing page 100, col. 1, first full paragraph.)

Further, the Examiner maintains that Woodford *et al.*, do suggest a formulation comprising an occlusive agent in an amount claimed instantly. The Examiner refers to the specification at page 4, first paragraph, wherein it is stated that "the occlusive agent is present in an amount sufficient to permit the formation of an occlusive layer or hydration barrier on the skin of the patient ... the amount of occlusive agent in the mousse composition may be up to approximately 55%," thus, because no lower limitation is specified by the specification, this amount includes zero percent. However, the Examiner contends that the Woodford reference

clearly teaches 2.0 grams of a non-emulsifying wax being present in the formulation, allegedly meeting the amounts of occlusive according to the present claims.

The Examiner further maintains that the formulations of Woodford *et al.* have occlusive properties or that occlusive properties in a foam would be achievable. The Examiner adds that there are numerous reasons for applying a polyester film to the skin, such as a method of controlling external influences on the skin. According to the Examiner, it appears that Woodford is applying a film to control external influences on the skin, thus being able to solely measure the efficacy and bioavailability of his composition.

The Examiner maintains that Woodford *et al.*, teach that "the precipitation of the wax from the solution produced a foam that collapsed on the skin as the wax re-dissolved at skin temperature." (citing, page 103, col. 2, first full paragraph) Thus, according to the Examiner, a wax that precipitates on the skin suggests an occlusive agent in the amounts according to the instant claims.

*Woodford et al. Distinguished*

Applicants reiterate that Woodford *et al.* do not teach or suggest an occlusive agent. The pending claims all require a formulation containing a specified amount of occlusive agent, i.e. "an amount sufficient to form an occlusive layer, on the skin, in use."

The present invention features an aerosol foam or mousse composition that includes a sufficient amount of occlusive agent to form an occlusive layer on the skin and able to enhance topical delivery of a pharmaceutical. When applied, the occlusive agent forms an occlusive layer on the skin resulting in a reduction in transepidermal water loss and increased skin hydration, which, in theory, increases skin permeability to effect enhanced skin penetration of a pharmaceutical. (*See, e.g.*, specification, pages 2-3 and 6-12.)

Applicants reiterate that Woodford, *et al.*, do not suggest providing an aerosol foam having any such manner of occlusive agent. In fact, Woodford, *et al.* resort to ***external means*** to provide for occlusion as discussed below.

Specifically, Woodford, *et al.*, explicitly describe occluding the application test sites by using polyester film to assess the efficacy and bioavailability of test formulations applied to the forearms of volunteers. (*See,* page 100, first column, last paragraph; Harding Declaration, paragraph 15) A polyester or food wrap film is often used when assessing the efficacy and bioavailability of an active ingredient in a composition. This type of cover provides occlusion, and the performance of active ingredients is normally enhanced when tested under occlusion. Woodford *et al.* use a polyester film for occlusion and not just as a protective barrier. In fact, Woodford *et al.* use a plastic guard to offer protection against external influences but not occlusion in a subsequent set of tests in the cited article. (Harding Declaration, paragraph 15) Notably, Woodford *et al.* are using an occlusion technique previously used with other products. A number of commercially available products use occlusion to achieve acceptable performance. Two such products, Emla Cream and Nicotine patches, use occlusive techniques to achieve efficacy. The consumer information sheet for Emla cream (submitted herewith as Appendix 5) stipulates the use of such a plastic food wrap or the like over the composition after application for this very purpose.

Although Woodford *et al.* teach using a wax, a wax is not synonymous with "occlusive agent." Woodford *et al.* teach using 2.0 g of a ***nonionic*** emulsifying wax (not "2.0g of non-emulsifying wax" as the Examiner states on page 4 of the Final Office Action. (Harding Declaration, paragraph 10) A non-ionic emulsifying wax is a suitable foaming agent for quick break foams such as the topical dosage corticosteroid quick break aerosol foam described by Woodford *et al.* Especially in the presence of dichlorodifluoromethane and dichlorotetrafluoroethane, an aqueous alcohol system incorporating a non-ionic emulsifying wax may be used to prepare a quick break foam provided the alcohol-water ratio is between approximately 50:50 and 70:30. (Harding Declaration, paragraph 11)

Despite the Examiner's contention, the term wax is not synonymous with occlusion. Wax is a term that describes general physical properties and physical states (*See, e.g.*, Lenick, *et al.* submitted herewith as Appendix 4). The formulations of Woodford *et al.* were occluded

with a polyester film. (Harding Declaration, paragraph 13) In short, Woodford *et al.* do not teach including an occlusive agent as claimed in the present application. Woodford *et al.* state that the actual nonionic emulsifying wax used was Polarwax A31 manufactured by Croda Chemicals. (Harding Declaration, paragraph 14) Information from Croda and the Cosmetic and Toiletries Bench Reference reveal that this wax is a mixture of cetostearyl alcohol and a polyoxyethylene derivative of a sorbitan fatty acid ester (*See, e.g.*, Appendix 4, submitted herewith). Neither a cetostearyl alcohol nor a polyoxyethylene derivative of a sorbitan fatty acid ester are considered occlusive agents. A polyoxyethylene derivative of a sorbitan fatty acid ester is a medium to high HLB surfactant with good water affinity. Cetostearyl alcohol, although a long chain alkane, has a hydroxyl group attached at the end of the chain. This imparts significant polarity and hydrophilicity to the molecule. Hence, this property would allow easy transmission of water across a film made from this material. Although the wax (Polarwax) of Woodford *et al.* is precipitated onto the skin is not occlusive. (Harding Declaration, paragraph 14)

**SUMMARY**

Woodford, *et al.*, must resort to an external device, i.e., polyester film to provide occlusion, indicative ***that the disclosed formulations themselves do not achieve such an effect.*** Therefore, the fact that Woodford, *et al.*, disclose certain components, e.g., a non-ionic emulsifying wax (at 2% by weight) used as a foaming agent (*See*, paragraph spanning pages 99-100 and page 103 , first full paragraph), does not equal teaching or suggesting the compositions according to the current claims having effective amounts of occlusive agents.

Again, the term wax is not synonymous with occlusion. Wax is a term that describes general physical properties and physical states (*See, e.g.*, Lenick, *et al.* submitted herewith as Appendix 4). The generally accepted classification for oils, waxes and butters is that the material is insoluble in water and is of the appropriate physical state. An example of such a

material is silicone wax 580 from Dow Corning. This material is insoluble in water, but is not occlusive as explained in the Dow Corning literature (submitted herewith as Appendix 5).

As the combination of Davis and Woodford, *et al.*, does not teach each and every element of the claims, the claims cannot be rendered unpatentable under 35 U.S.C. §103(a) by the combination.

***Rejection under 35 U.S.C. §103(a) over Davis, in view of Woodford, et al., and further in view of Jones***

Claims 1-14, 16-18, 20-30, and 32-33 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis and Woodford, *et al.*, as applied above and further in view of Jones, *et al.* (WO 96/27376). The Examiner admits that the combination of Davis and Woodford, *et al.* previously discussed lacks the specific emulsifier recited in dependent claims 11 and 26. Jones *et al.* teach a corticosteroid containing quick break foam, and is relied upon specifically for teaching the emulsifier polysorbate 60.

The deficiencies of combining Davis and Woodford, *et al.* is discussed in detail above. The inclusion of the specific emulsifier polysorbate 60 taught by Jones in no way cures these deficiencies. Applicants respectfully submit that the Examiner is of the same opinion as noted by the following reasoning:

> Applicant's argument that the Jones *et al.* does not cure the deficiencies of Davis and Woodford because Jones is relied upon for the particular emulsifier in dependent claims 11 and 27 are not convincing because contrary to applicant's assertion, the amendment ***to claims 1, 18, and 20*** have not overcome the prior art rejection.

***Rejection under 35 U.S.C. §103(a) over Davis in view of Woodford, et al., and further in view of Gers-Barlag***

Claims 1-10, 12-18, 20-26, 28-33 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis and Woodford, *et al.*, as applied above and further in view of Gers-Barlag, *et al.* (US 5,833,960).

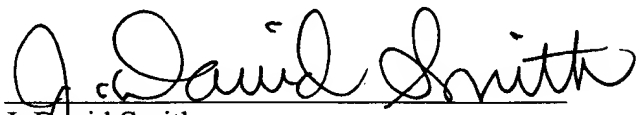
Gers-Barlag *et al.* is directed to light protection preparations, and more particularly directed to "after-foaming" preparations, which foam ***after*** application to the skin. (*See, e.g.,* column 1, lines 8-10; column 4, lines 34-56; column 8, line 64 through column 9, line 2.) This reference is relied upon by the Examiner for particular amounts of aqueous solvent or propellant, as recited in dependent claims 13 and 17, respectively, and for providing particular solvents recited in dependent claims 15 and 30.

Again, the deficiencies of combining Davis and Woodford, *et al.* are of record and reiterated in detail above. Particular amounts of aqueous solvent or propellant, or particular solvents, as taught by Gers-Barlag, likewise does not cure these deficiencies. Applicants respectfully submit that the Examiner is of the same opinion as noted by the following reasoning: "contrary to Applicant's assertion, ***the amendment to claims 1, 18, and 20 have not overcome the prior art rejection***."

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 468452000300.

Respectfully submitted,

Dated: May 1, 2003

By: 

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